Diffuse Cystic Lung Disease at High-Resolution CT

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OBJECTIVE. This article will illustrate and describe the spectrum of diseases associated with air cysts at high-resolution CT (HRCT).

CONCLUSION. HRCT is an important modality in the evaluation of interstitial lung disease to include cystic lung disease. Although most commonly associated with lymphangioleiomyomatosis or Langerhans cell histiocytosis, cystic lung disease is increasingly being recognized as a feature of other entities. Awareness of the spectrum of HRCT findings associated with these diseases may help the trained observer narrow the differential diagnosis.

Keywords: cystic lung disease, high-resolution CT, interstitial lung disease, Langerhans cell histiocytosis, lymphangioleiomyomatosis

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Many diffuse lung diseases may manifest cysts as the primary abnormality, although lymphangioleiomyomatosis and Langerhans cell histiocytosis (LCH) are the most common to present with diffuse lung cysts [1, 2]. Awareness of these conditions and their distinguishing imaging features may lead to the correct diagnosis. In a retrospective study of 77 patients with proven chronic cystic lung disease and 15 patients with emphysema [3], a correct first-choice diagnosis based on high-resolution CT (HRCT) findings alone was made in 80% of patients; this study was not limited to the three previously mentioned diffuse cystic lung diseases but also included other disease entities such as desquamative interstitial pneumonia (DIP) and usual interstitial pneumonia in which cysts or honeycomb lung may be seen on a background of ground-glass opacities or fibrotic change [3]. This pictorial essay will illustrate and describe the spectrum of diffuse cystic lung diseases, including several rare entities, and the pertinent differentiating HRCT and pathologic features.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare disorder occurring almost exclusively in women of childbearing age. Globally, lymphangioleiomyomatosis associated with tuberous sclerosis complex is 5- to 10-fold more common than sporadic lymphangioleiomyomatosis [2]. Recent evidence suggests that the angiomyolipomas seen in patients with lymphangioleiomyomatosis are related perivascular epithelioid cell tumors ("PEComas") that result from the dysregulated mammalian target of rapamycin signaling [4]. Lymphangioleiomyomatosis is characterized by smooth-muscle cell proliferation in the pulmonary interstitium affecting vessels, airways, lymphatics, alveolar septa, and pleura. The cysts in lymphangioleiomyomatosis are thought to arise from air trapping resulting from peribronchiolar proliferation. Lymphatic obstruction may result in chylous pleural effusion, chylous ascites, or both. Spontaneous or recurrent pneumothorax may be the presenting finding in up to 50% of patients with lymphangioleiomyomatosis. Involvement of the pulmonary vessels may lead to thickened arterial walls and venous occlusion [1].

Characteristic HRCT features of lymphangioleiomyomatosis are diffuse thin-walled cysts surrounded by normal lung without regional sparing (Figs. 1–3). Cysts are usually 2–5 mm but can be as large as 25–30 mm. Cysts are typically round or ovoid, but they may become polygonal with severe parenchymal involvement. Small centrilobular nodules corresponding to hyperplastic muscle or pneumocyte hyperplasia have been reported. Focal ground-glass opacities may be due to smooth-muscle proliferation, hemosiderosis, or pulmonary hemorrhage (Fig. 3). Lymphatic obstruction may cause septal thickening.

Pulmonary Langerhans Cell Histiocytosis

Pulmonary LCH is a smoking-related lung disease, with 80–100% of cases seen in patients

who smoke or have a history of smoking. LCH occurs most frequently in young adults [5]. Peribronchiolar infiltration of Langerhans and inflammatory cells results in bronchiolocentric stellate interstitial nodules [5]. The nodules may subsequently cavitate and form thick- and thin-walled cysts thought to represent enlarged airway lumina [5] (Figs. 4–9). Frequently, both nodules and cysts are seen. Cysts may be round but are often irregular, bilobed, cloverleaf-shaped, or bizarre shapes. Irregular cysts, cysts with nodules, and upper zone predominance with sparing of the costophrenic angles are features that distinguish LCH from lymphangioleiomyomatosis.

Also in the spectrum of smoking-related interstitial lung disease, DIP can be associated with cysts (Figs. 10 and 11). On open lung biopsy, these small cysts are shown to represent bronchiolectasis and dilated alveolar ducts [6]. In the later stages of DIP, cysts may also represent early centrilobular emphysema or honeycombing [6]. Centrilobular emphysema represents the permanent destruction of bronchiolar walls with resultant enlargement of the airspaces distal to the terminal bronchiole [3]. The distinguishing features of centrilobular emphysema include the lack of a perceptible cyst wall and the central location of the vascular structures [3].

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia (LIP) occurs in association with Sjögren syndrome most commonly and also with AIDS, primary biliary cirrhosis, Castleman disease, systemic lupus erythematosus, and autoimmune thyroid disease. Pathology reveals a diffuse interstitial proliferation of small lymphocytes and plasma cells. The perilymphatic interstitium—including the peribronchovascular interstitium, interlobular septa, and pleura—is most affected. HRCT shows ground-glass opacities, poorly defined centrilobular nodules, and thin-walled cysts with a basal predominance (1–30 mm). Although the cysts may vary in size, often being smaller than 30 mm (Fig. 12), they are typically less numerous than in lymphangioleiomyomatosis or LCH. Additional HRCT findings reported in LIP include peribronchovascular thickening, interlobular septal thickening and subpleural nodules, lymphadenopathy, and areas of consolidation [7] (Fig. 13).

Follicular Bronchiolitis

Follicular bronchiolitis is in the spectrum of lymphoproliferative processes that includes LIP; however, in follicular bronchiolitis, involvement is limited to the airways. Focal hyperplasia of bronchus-associated lymphoid tissue may compress the bronchioles resulting in airflow limitation [8]. At HRCT, 3- to 12-mm centrilobular or peribronchial nodules are the most common findings. Thin-walled cysts are a less common feature (Fig. 14). Follicular bronchiolitis is distinguished from LIP by the degree of adjacent parenchymal involvement, with focal peribronchial lymphoid hyperplasia occurring in follicular bronchiolitis and with more widespread interstitial involvement in LIP.

Amyloidosis

Amyloidosis is characterized by extracellular deposition of various proteins in β–pleated sheets and may be localized (10–20%) or systemic (80–90%) [9]. Systemic amyloidosis is then classified as primary (i.e., associated with multiple myeloma or macroglobulinemia) or secondary (i.e., associated with rheumatoid arthritis, tuberculosis, Crohn disease, cystic fibrosis, or Mediterranean fever). HRCT findings of pulmonary amyloidosis include nodules, interlobular septal thickening, honeycombing, ground-glass opacities, and lymphadenopathy [9] (Fig. 15). Pulmonary cysts are rare and are most often described with localized amyloidosis in association with Sjögren syndrome [10]. The proposed mechanisms of cyst formation include narrowing of the airway due to inflammatory cells with a check-valve mechanism, disruption of fragile alveolar walls due to amyloid deposition, and destruction of alveolar walls due to ischemia from vascular infiltration by amyloid [10].

Light-Chain Deposition Disease

Light-chain deposition disease (LCDD) occurs in middle-aged patients with a mean age of 67 years and commonly involves the kidneys. Although lung involvement is rare, LCDD can result in respiratory failure and require lung transplantation [11]. Seventy-five percent of LCDD cases occur in association with multiple myeloma or macroglobulinemia [11]. The light chains are secreted by a plasma clone and deposit in the alveolar walls, small airways, and vessels. HRCT manifestations most commonly include nodules, lymphadenopathy, and cysts. Cyst formation is believed to correspond to dilation of the small airways (Fig. 16).

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome is a rare autosomal-dominant disorder characterized by

TABLE 1: Distinguishing Features of Diffuse Cystic Lung Diseases on High-Resolution CT (HRCT)

Diagnosis	Clinical Features	Distinct HRCT Features	Associations
Langerhans cell histiocytosis	Smoker	Early centrilobular nodules, sparing of costophrenic angle	Pulmonary hypertension
Lymphangioleiomyomatosis		Diffuse uniform cysts, chylous effusions, no nodules	Serum VEGF-D, angiomyolipoma
Sporadic	Premenopausal women		
Associated with tuberous sclerosis complex	Seizures, skin lesions		
Follicular bronchiolitis and LIP	Sjögren disease, cardiovascular disease, AIDS	Perivascular cysts	Lymphoproliferative disorder, lymphoma
Amyloidosis, LCDD	Renal failure, Sjögren disease	Cysts and larger nodules[a]	Multiple myeloma, macroglobulinemia
Birt-Hogg-Dubé syndrome	Skin lesions	Basilar subpleural lentiform cysts	Renal neoplasms, colonic polyposis
Cystic metastases	History of malignancy, positive CA-125	Peripheral, hematogenous	

Note—VEGF-D = vascular endothelial growth factor D, LIP = lymphocytic interstitial pneumonia, LCDD = light-chain deposition disease, CA-125 = cancer antigen 125.
[a]Can be cancerous.

fibrofolliculomas distributed over the face, neck, and upper trunk; renal tumors ranging from benign oncocytomas to renal cell carcinomas; colonic polyposis; and chorioretinal disease [12]. The limited information on HRCT findings in patients with Birt-Hogg-Dubé syndrome reveals bullous emphysema, thin-walled cysts (80%), and pneumothorax (Figs. 17 and 18). Pathologically, the cysts are often elongated and subpleural in distribution, with the total extent of lung involvement being less than 30% [13].

Cystic Pulmonary Metastatic Disease

Cystic pulmonary metastases occur most frequently in tumors of epithelial origin and less frequently in tumors of mesenchymal or hematopoietic origin [14]. Mesenchymal neoplasms in which pulmonary cysts have been reported include leiomyosarcoma [14] (Fig. 19), synovial cell sarcoma [14], epithelioid cell sarcoma [15], and endometrial stromal sarcoma (ESS) [16] (Fig. 20). The appropriate history of primary malignancy is critical to suggest this diagnosis. Although cysts are a rare presentation of ESS metastases, immunostains are useful in distinguishing metastatic ESS from lymphangioleiomyomatosis: HMB45 antibody and CD34 are commonly positive in lymphangioleiomyomatosis and negative in ESS [16].

Conclusion

The differential diagnosis of diffuse cystic lung disease is more extensive than previously described and may be organized on the basis of clinical history, serologic evaluation, and the HRCT appearance of the cysts and ancillary HRCT findings (Table 1). Although lymphangioleiomyomatosis and LCH are the most frequently encountered causes of thin-walled cysts at HRCT, this pictorial essay reviews imaging and pathologic features that may suggest an alternative diagnosis.

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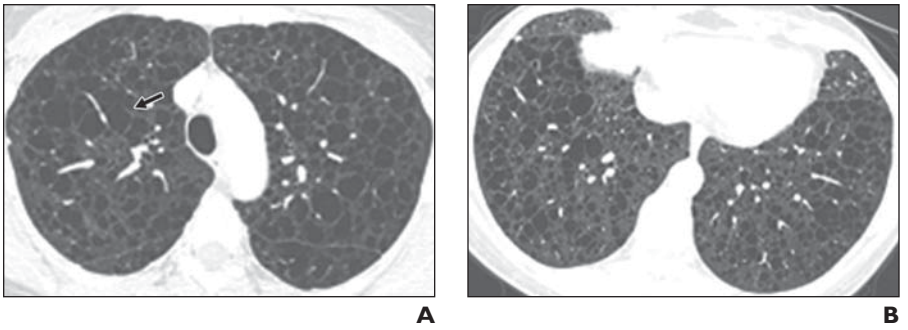

A **B**

Fig. 1—Lymphangioleiomyomatosis.
A and **B,** High-resolution CT images show characteristic appearance of lymphangioleiomyomatosis: diffuse thin-walled cysts surrounded by normal lung. Cysts are usually 2–5 mm but can be as large as 25–30 mm. Cysts are typically round or ovoid but may become polygonal (*arrow,* **A**) when parenchymal involvement is severe.

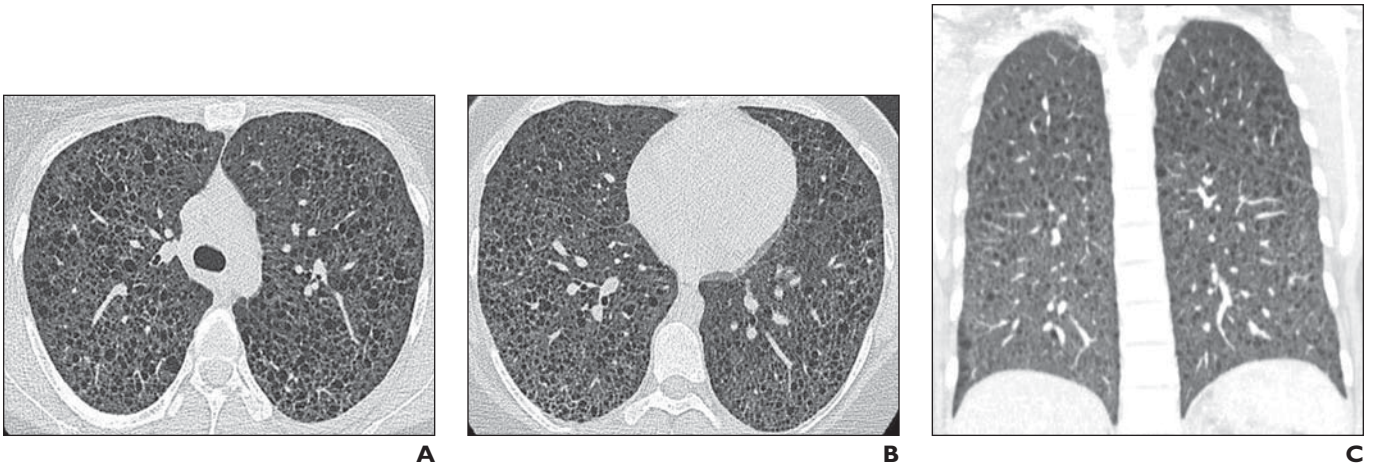

Fig. 2—Lymphangioleiomyomatosis.
A and **B,** High-resolution CT images show diffuse thin-walled cysts and intervening normal lung. These cysts are round or ovoid and relatively uniform in size.
C, Coronal reformatted image shows diffuse involvement with lack of regional sparing and involvement of costophrenic sulci.

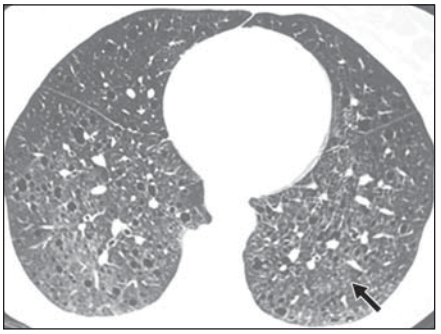

Fig. 3—Lymphangioleiomyomatosis. High-resolution CT image shows small thin-walled cysts with additional imaging features including small centrilobular nodules (*arrow*) and focal areas of ground-glass opacity. Although not shown here, septal thickening is another imaging feature of lymphangioleiomyomatosis.

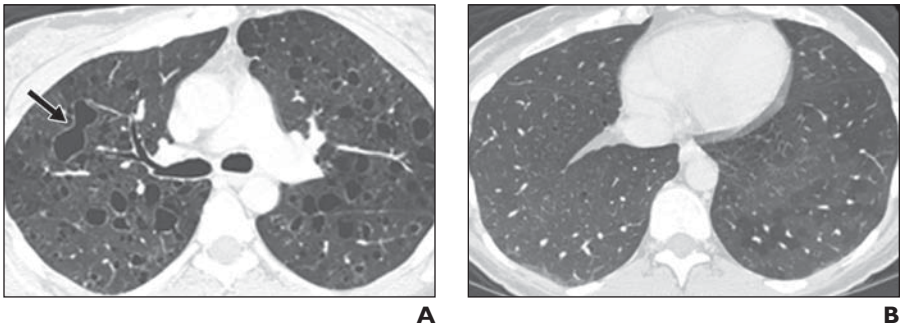

Fig. 4—Langerhans cell histiocytosis.
A, High-resolution CT image shows thin-walled cysts. Cysts may be round but are frequently irregular, bilobed (*arrow*), cloverleaf-shaped, or bizarre shapes. Note striking upper lobe predominance.
B, High-resolution CT image shows sparing of lung bases.

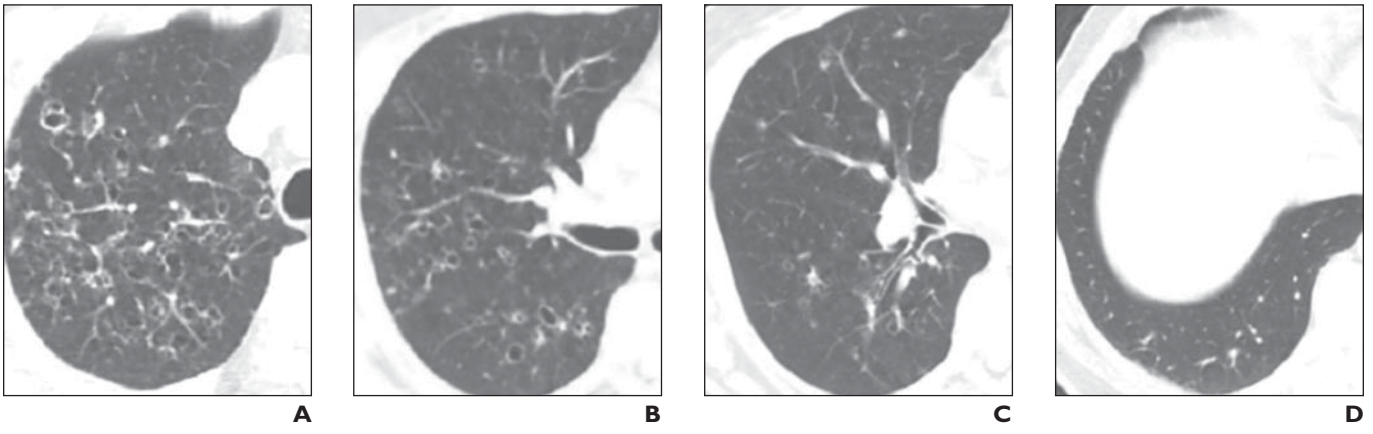

Fig. 5—Langerhans cell histiocytosis (LCH).
A–D, High-resolution CT images show thin-walled cysts and nodules. Again, note striking upper lobe predominance and, in **D**, sparing of costophrenic angles, one feature that can be used to distinguish LCH from lymphangioleiomyomatosis.

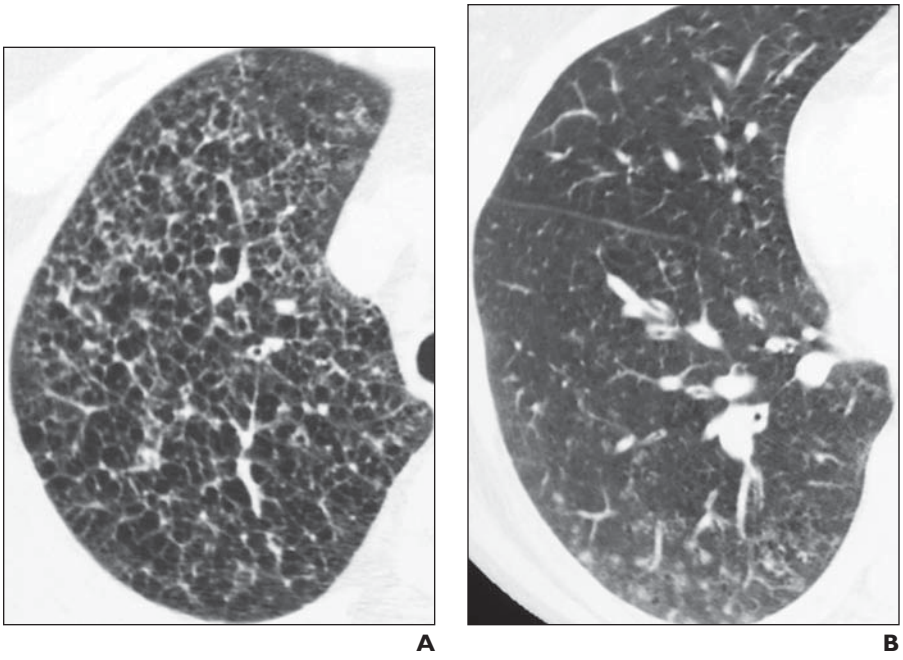

Fig. 6—Langerhans cell histiocytosis in female smoker.
A, High-resolution CT (HRCT) image shows thick- and thin-walled cysts of various shapes. Cysts have upper zone predominance.
B, Located more inferiorly than cysts, centrilobular nodules are predominant feature on HRCT image.

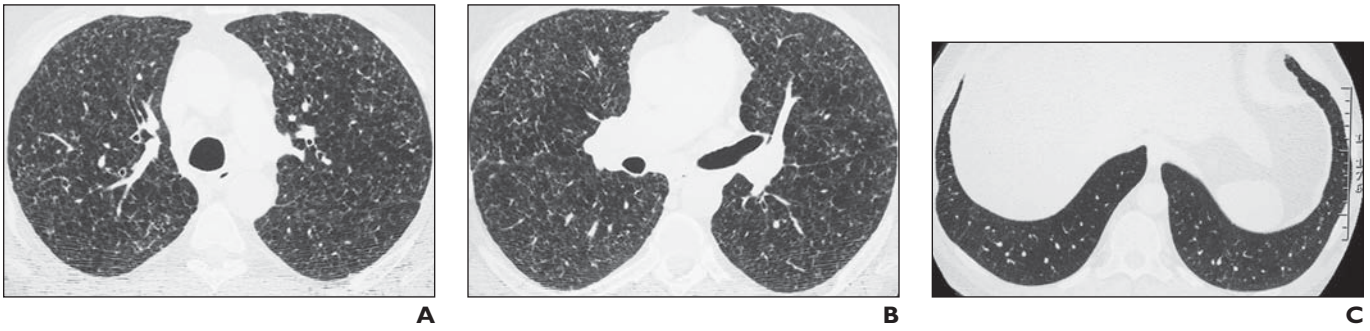

Fig. 7—Langerhans cell histiocytosis in 50-year-old male smoker.
A and **B,** High-resolution CT images show innumerable thin-walled cysts with little intervening normal lung parenchyma.
C, Again, note sparing of costophrenic angles on high-resolution CT image.

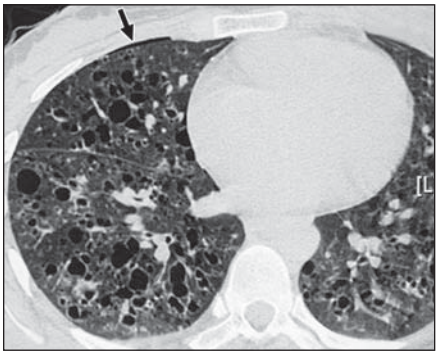

Fig. 8—Langerhans cell histiocytosis. Thin- and thick-walled cysts of various shapes and sizes are dominant feature. There are also scattered nodules. Note tiny right anterior pneumothorax (*arrow*).

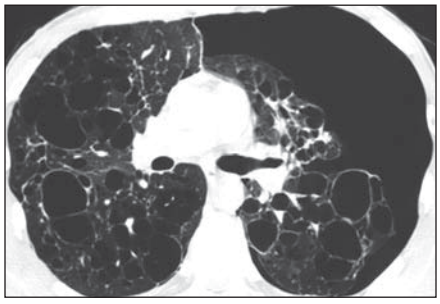

Fig. 9—Langerhans cell histiocytosis in 25-year-old male heavy smoker presenting with large left pneumothorax. Again, HRCT image shows thin- and thick-walled cysts of various shapes and sizes.

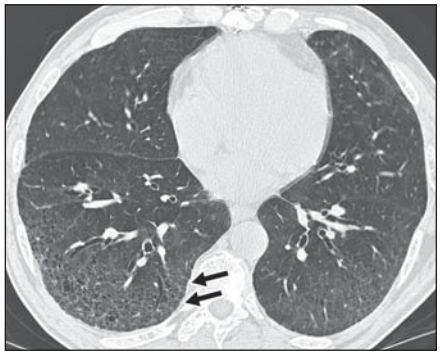

Fig. 10—Desquamative interstitial pneumonia. High-resolution CT image shows small cysts surrounded by ground-glass opacity and rare subpleural linear opacities (*arrows*).

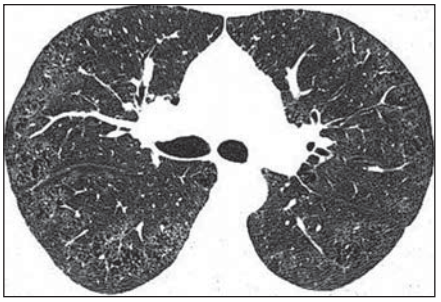

Fig. 11—Desquamative interstitial pneumonia on high-resolution CT image shows numerous small peripheral cysts surrounded by ground-glass opacity.

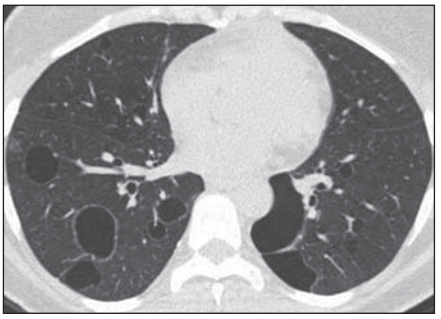

Fig. 12—Lymphocytic interstitial pneumonia in patient with Sjögren syndrome. High-resolution CT image shows thin-walled cysts of various sizes, some of which are subpleural (1–30 mm).

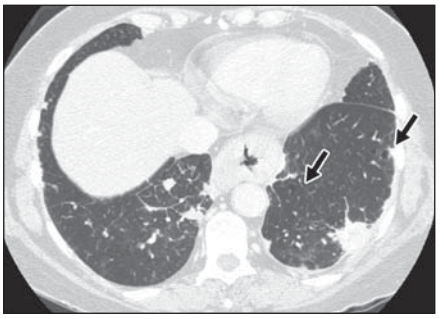

Fig. 13—Lymphocytic interstitial pneumonia (LIP). High-resolution CT image shows additional findings seen in patients with LIP including peribronchovascular thickening, interlobular septal thickening, subpleural nodules, and areas of consolidation. Cysts (*arrows*) in this patient are very small.

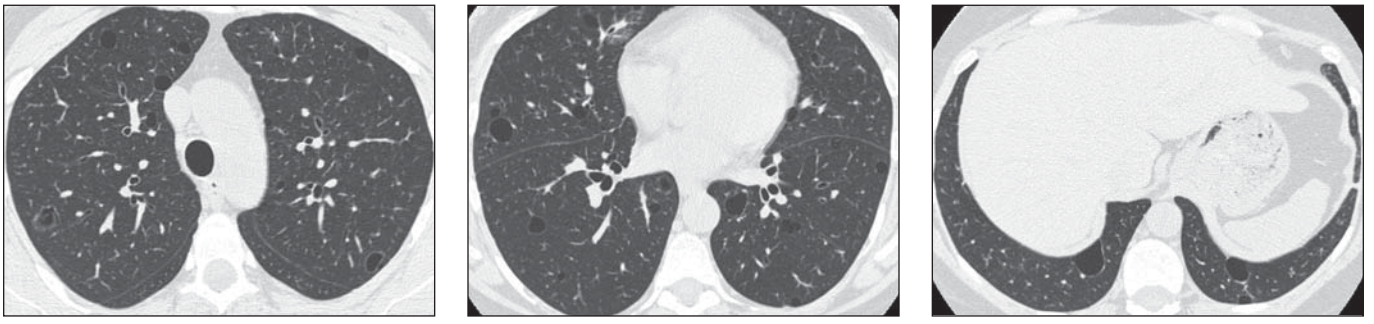

Fig. 14—Follicular bronchiolitis.
A–C, High-resolution CT images show thin-walled cysts (3–12 mm). Note amount of intervening normal lung parenchyma, feature distinguishing follicular bronchiolitis from lymphocytic interstitial pneumonia, the latter of which generally has more widespread interstitial involvement.

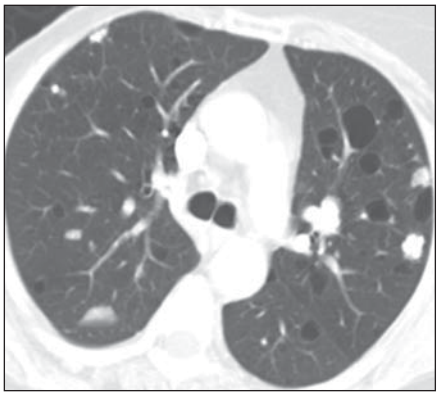

Fig. 15—Amyloidosis in patient with Sjögren syndrome. High-resolution CT image shows cysts and nodules. Cysts may occur secondary to lymphocytic interstitial pneumonia in association with Sjögren syndrome or peribronchiolar amyloid deposition. Although not shown in this case, findings suggestive of pulmonary diffuse interstitial amyloidosis include interlobular septal thickening, subpleural micronodules, ground-glass opacity, and honeycombing.

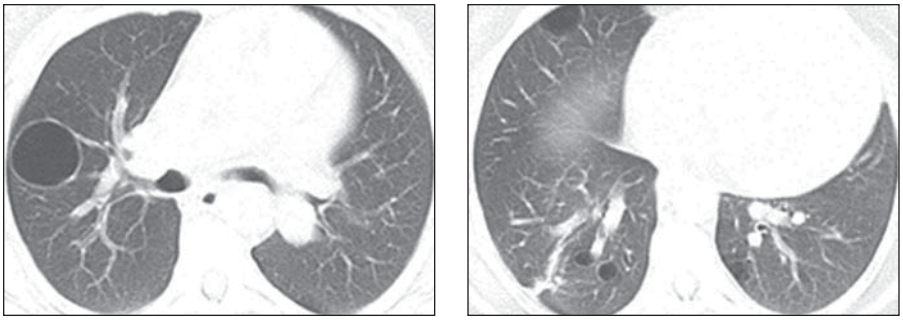

Fig. 16—Light-chain deposition disease (LCDD).
A and **B,** Imaging manifestations of LCDD most commonly include cysts, as shown on these high-resolution CT images; nodules; and lymphadenopathy. Cyst formation is believed to correspond to dilatation of small airways.

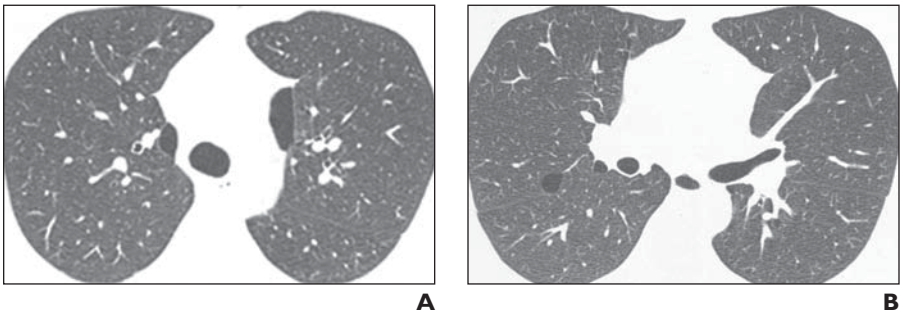

Fig. 17—Birt-Hogg-Dubé syndrome.
A and **B,** Imaging manifestations of Birt-Hogg-Dubé syndrome include bullous emphysema; thin-walled cysts, as shown on these high-resolution CT images; and pneumothorax.

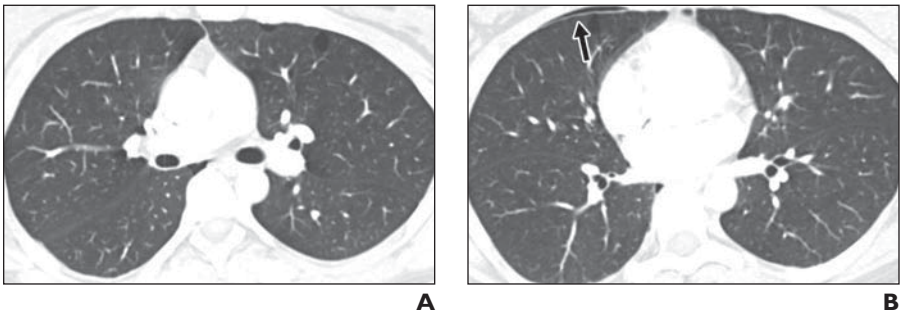

Fig. 18—Birt-Hogg-Dubé syndrome.
A, High-resolution CT image shows scattered thin-walled subpleural cysts.
B, High-resolution CT image shows that patient presented with small right pneumothorax (*arrow*).

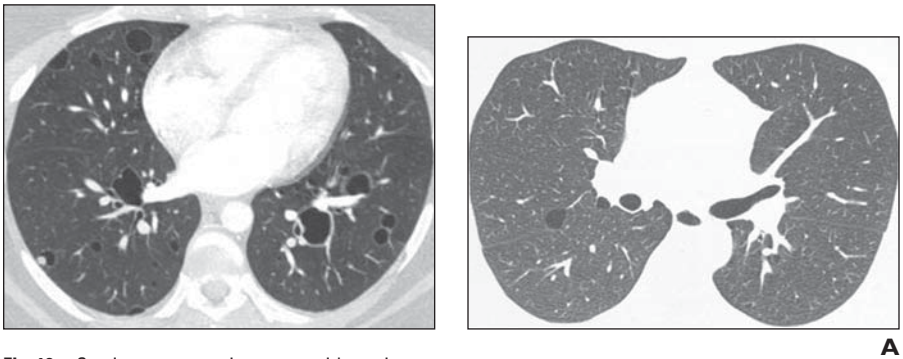

Fig. 19—Cystic metastases in woman with uterine leiomyosarcoma metastases. CT image shows multiple thin-walled cysts of various shapes and sizes.

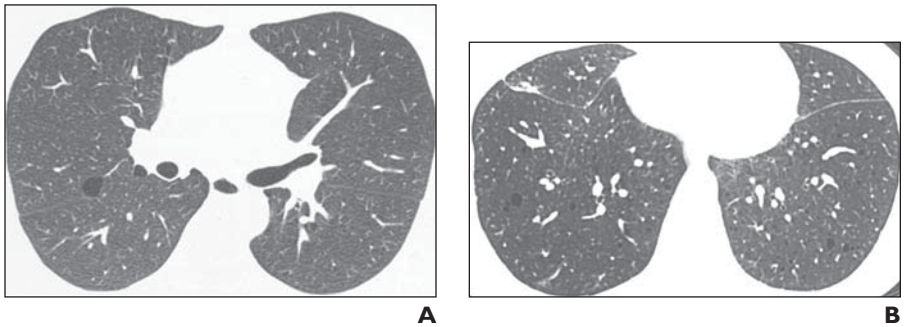

Fig. 20—Cystic metastases in woman with metastatic endometrial stromal sarcoma.
A and **B,** CT images show multiple small (1–2 cm) thin-walled cysts.

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